Title:

Pseudokinases: a tribble-edged sword

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Abstract

Advances in the understanding of the Tribbles family of pseudokinases (TRIB1, TRIB2 and TRIB3) reveal the potential of these proteins as valuable biomarkers of disease diagnosis, prognosis, prediction and clinical strategy. In their role as signalling mediators and scaffolding proteins TRIBs lead to changes in protein stability and activity which impact on diverse cellular processes such as proliferation, differentiation, cell cycle and cell death. We review the role of TRIB proteins as promising therapeutic targets with an emphasis on their role in cancer and as biomarkers with potential application across diverse pathological processes.

Introduction

Pseudokinases represent the most well understood class of pseudoenzymes, and carry out many critical non-enzymatic roles in physiological and pathological processes. The widely-studied Tribbles (TRIB) family of serine/threonine pseudokinases function as important signalling mediators and scaffold subunits via the binding and modulation of several signalling molecules, including kinases, phosphatases, transcription factors and components of the ubiquitin proteasome system.

TRIBs have confirmed and proposed functions in a number of cancers, and advances in the understanding of both the normal and malignant biology of TRIBs and other pseudokinases reveal the potential of these proteins as valuable biomarkers of disease diagnosis, prognosis, prediction and clinical strategy. This was first recognised in kidney disease, where in the kidney transplantation setting, TRIB1 was established as a biomarker of immune-mediated chronic allograft failure associated with a poor prognosis[1]. Another striking example is in blood cancer, where there is a correlation between high expression of TRIB2 and anti-apoptotic BCL-2[2], which confers sensitivity to the BH3 mimetic Venetoclax[3], an emerging novel agent for blood cancer treatment, and highlighting the potential of TRIB2 as a predictive biomarker for treatment response in blood cancer patients.

Further to this, recent studies have addressed the pharmacological targeting of pseudoenzymes with pre-approved drugs, repurposing these compounds to achieve novel secondary on-target effects by rational selection of potential compounds by function. This approach to drug-discovery highlights the potential of utilizing pre-existing, repurposed treatments to achieve positive clinical outcomes while minimizing the time and financial constraints traditionally associated with drug development.

Pseudokinases

Protein kinases have long since been recognized for their vital roles in the regulation of most eukaryotic processes and have been demonstrated to be dysregulated in multiple conditions including cancers and neurodegenerative diseases. The primary role of protein kinases is to catalyse transfer of a phosphate group from ATP to its substrate, a process which is mediated by a highly conserved kinase

domain fold, thus inherently assigning these enzymes a secondary role as an effective and precise protein scaffold[4].

Of more than 500 protein kinases identified in the human kinome, around 10% have been subsequently categorised as 'pseudokinases'[5]. Pseudokinases are vital in the regulation of diverse cellular processes, and have known associations with a number of key biological pathways often found dysregulated in disease. These pseudoenzymes are less well defined but lack canonical phosphotransferase activity and are found throughout distinct kinase subfamilies, suggesting diverse evolutionary roots which have been well-reviewed elsewhere[6] and in this special issue. Pseudokinases can be further categorized into several groups by their missing residues, and almost half have been reported to show residual ATP-binding activity, though this is an area of some debate and highly controversial. The pseudokinase JH2 domain of JAK2, for example, binds ATP and shows some weak catalytic activity. It is unclear whether this is important for JAK2 function, and indeed disruption of ATP-binding in wild type JAK2 does not affect activation, however ameloriates hyperactivation of the JAK2 V617F mutant[7], incidentally highlighting the JH2 domain as an interesting potential therapeutic target.

Despite lacking canonical phosphotransferase activity, pseudokinases play key roles in normal and disease biology via their function as signal transduction mediators and as protein scaffolds, often promoting degradation or stability of their pseudo-substrates by facilitating ubiquitination. In the case of the CAMK subfamily 'Tribbles', a C-terminal tail docking site with a conserved DQLVP motif regulates the activity of COP1 E3 ubiquitin ligase[8,9] and thus the ubiquitination and subsequent degradation of target substrates, whereas in other instances TRIB has led to increased substrate stability by inhibiting ubiquitination[10]. Additionally, a MEK1 binding site confers a signal transduction role in the MAPK pathway. Several pseudokinases have been well-studied in human cells including JAK2 (which contains both active kinase and pseudokinase domains)[11], the RAF/mitogen-activated protein

kinase (MEK) modulators, ErbB3/HER3[12] and the TRIB family, and many of the 48 pseudokinases found in humans have distinct homologues in popular models such as *D. Melanogaster* and *C. Elegans*.

Tribbles in normal physiology

The three Tribble pseudokinases (TRIB1, TRIB2 and TRIB3) found in the human genome are homologues of the *Drosophila* pseudokinase 'Tribbles' (*Trbl*), and indeed many interactions between Tribbles family proteins and their partners are conserved across species. *Drosophila* Trbl induces degradation of the C/EBPα transcription factor homolog slbo and the CDC25 phosphatase homolog String via the proteasome pathway[13], thereby regulating cell differentiation, proliferation, migration and growth, and interacts with the proto-oncogene AKT[14].

Evolving from a common ancestor[13], mammalian TRIB pseudokinases are three-domain proteins containing an N-terminal PEST region, a highly atypical bi-lobed pseudokinase core (lacking one or more canonical catalytic residues) and a C-terminal tail (Figure 1). As with other members of the pseudokinase family, there is some debate surrounding the attribution of ATP-binding activity to the pseudokinase core of TRIB proteins, and subsequently the relevance of residual ATP-binding affinity for function. While TRIB1 is generally recognized as being incompatible with ATP binding which has been confirmed by structural studies[9,15], the ATP binding attribution to TRIB2 remains controversial. Bailey *et al.* demonstrated a low affinity of TRIB2 for ATP [16], an interaction reliant upon the conserved Lys^{90} residue, while Murphy *et al.*[17] conversely saw no nucleotide binding properties of a number of pseudokinases including TRIB2 and clarification of the ATP-binding status of TRIB2 requires further structural studies. Whether ATP-binding occurs or not, it is not clear that it serves a biological function as there is currently no known association between TRIB function and catalytic activity.

Within the C-terminal tail, MEK1 and COP1 binding sites result in TRIB-mediated modulation of the MAPK/ERK signal transduction pathway via increased ERK phosphorylation[18], and proteosomal degradation by interaction with COP1 E3 ubiquitin ligase[19]. The pseudokinase domain facilitates this

E3-mediated degradation of target substrates by anchoring target proteins in close proximity to the E3 ligase and of the many roles of TRIB family pseudokinases, COP1-dependent degradation of the transcription factor C/EBPα is the best understood[20]. Several studies have provided valuable insight into the mechanism of TRIB-mediated degradation of C/EBPα by COP1[15,21,22]. It was demonstrated by Jamieson et al. that a significant conformational change of TRIB1 occurred upon C/EBPα binding to the pseudokinase core. This conformational change induced allosteric changes which facilitated the undocking of the C-terminal COP1 binding motif from the core, releasing autoinhibition to allow for COP1 recruitment and COP1-mediated ubiquitination and degradation of C/EBPα (Figure 2).

TRIB pseudokinases can also stabilise protein substrates by modulating the ubiquitin proteasome system as has been demonstrated for TRIB3-mediated inhibition of PML-RARα ubiquitination[10] . Modulation of pro-survival AKT/FOXO signalling has also been demonstrated, though the molecular mechanisms are yet to be fully understood and different TRIB family members appear to have different roles in this pathway (Figure 3); TRIB2 has been shown to enhance AKT signalling and promote drug resistance in cancer cells[23], while TRIB3 has been shown to inhibit AKT phosphorylation in neuronal cells, driving cell death in Parkinson's disease[24]. The integration of TRIB proteins with signal transduction and degradation pathways (Figure 3) confers multifactorial roles for each family member which are highlighted in **Error! Reference source not found.**.

One of the first identified roles of mammalian TRIB proteins was in glucose regulation[34] and lipid metabolism[37], where it was shown that TRIB3 contributes to insulin resistance by functioning as a negative modulator of AKT, and stimulated lipolysis through its association with COP1 E3 ligase. The first role for TRIB proteins in haematopoiesis, showed that TRIB2 could control the maturation and function of the myeloid and lymphoid lineages in response to cytokines including SCF, G-CSF, GM-CSF, and M-CSF[20]. Differential expression of the three TRIB pseudokinases in haematopoietic cells highlights non-redundant and lineage-specific functions in this system; TRIB1 is expressed most highly

in the myeloid lineage, TRIB2 in the lymphoid lineage and TRIB3 consistently across all haematopoietic cells[41].

Interactions between TRIBs and C/EBP transcription factors (C/EBPα, β, γ, δ, ε, ζ) underpin their importance in cell development and differentiation, as C/EBPs regulate the expression of a diverse spectrum of target genes[43]. In the haematopoietic system, TRIB1 and TRIB2 mediate degradation of the C/EBPα p42 isoform via polyubiquitination of lysine 48[20], which blocks neutrophil differentiation and concurrently increases differentiation of eosinophils, monocytes and macrophages. This demonstrates the necessity for a tightly-regulated balance of TRIB expression in normal myeloid haematopoiesis[39,40]. This is supported by recent studies showing that TRIB1 regulates early eosinophil lineage commitment and cell identity by integrating its role in C/EBPα degradation with IL-5 signalling[40], and there is strong evidence implicating a role for TRIB3 in quiescence of HSCs[44].

By regulating the activity and degradation of proteins including MEK1, MAPKs (p38, ERK, JNK), AKT, CDC25, ATF, NF-κB and Wnt/β-catenin TRIBs also regulate cellular function via protein interactions, in addition to control of haematopoietic cell development. TRIB1 plays a critical role in macrophage migration and driving the polarization and differentiation of M2-like macrophages[42] and eosinophils. TRIB proteins regulate innate inflammation signalling[38] via their interaction with NF-κB.

When we consider then the plethora of processes in which TRIB proteins and indeed many pseudokinases are involved, it is not difficult to appreciate the pathological effects which are observed upon their dysregulation.

TRIB pathologies

As with their catalytically active counterparts many pseudokinases are dysregulated in diseases, and TRIB expression can be induced by a range of cellular stresses and mitogens[44,45]. Consequently, TRIBs have been shown to play multifactorial roles in numerous cancers, as well as being linked to drug resistance via pro-survival and anti-apoptotic pathways[2,23]. Current knowledge indicates both oncogenic and tumour suppressive roles of the TRIB family, dependent on family member and cellular

context. **Error! Reference source not found.** highlights some of the known mechanisms by which TRIB proteins act in various cancer subtypes. Also outlined are a selection of kinase inhibitors which have been tested, either experimentally or by clinical trial, in the indicated type as these represent a promising route of investigation with respect to TRIB targeting, as will be discussed in more detail later.

The best understood pathway by which TRIBs promote oncogenesis is their role in degradation of C/EBP transcription factors. TRIB1 and TRIB2 degrade the C/EBPα p42 isoform resulting in excess p30, a mechanism that mimics what occurs in acute myeloid leukaemia (AML) patients with CEBPA mutations[68]. This mechanism of TRIB-mediated degradation of C/EBPα has a key role in the pathogenesis and therapeutic response of acute promyelocytic leukaemia, a subtype of AML expressing PML-RARα[47]. Indeed TRIB3 also has an important role mediating acute promyelocytic leukaemia tumorigenesis and treatment response via is stabilizing effect on the driver oncogene PML-RARα[10]. TRIB2 mRNA expression has been associated with an AML poor prognostic subgroup characterised by a dysregulated C/EBPα gene signature[20], but it is not associated with the good prognostic CEBPA-mutant subgroup, confirming the clinical importance and validation of TRIB2 mechanism. Interestingly, p30 drives AML only in the presence of p42[69], likely due to the requirement for p42-directed myeloid differentiation for formation of leukaemia stem cells and myeloid leukaemia initiation. Thus, although not mutated itself in AML, TRIB2 represents a highly promising therapeutic target in AML with potential application across heterogeneous molecular and cytogenetic subgroups.

Furthermore, TRIBs are known to regulate the Ras-Raf-MEK-ERK mitogen activating kinase pathway, which has a well-documented role in signal transduction in both normal and malignant cells[70], and components of this pathway and it's upstream receptors are often found aberrantly expressed or mutated in human cancers[71]. In line with this, this pathway is strongly associated with haematopoietic cell proliferation and drug resistance in AML, and is regulated via the interaction of TRIBs with MEK1 to drive increased phosphorylation of ERK. Consistent with this, an R107L substitution in TRIB1 has been shown to increase both ERK phosphorylation and C/EBPα degradation in human Down syndrome-related acute megakaryocytic leukaemia beyond that observed in cells carrying wild type TRIB1[72] . Drug resistance has also been seen to be conferred by TRIB2-related overexpression of anti-apoptotic BCL-2, which increases relapse and chemoresistance by promoting proliferation and blocking apoptosis[2].

Analysis of publicly available RNAseq data from the Human Protein Atlas highlights the variability of TRIB expression across cancer subtypes, and the significant upregulation of TRIB family members in many. However it is important to note that both published[49] and unpublished data demonstrate that TRIB roles, and therefore suitability as a biomarker in disease, are more accurately related to protein expression levels and thus this differential expression must be confirmed and analysed at the protein level.

TRIB dysregulation is not limited to cancer pathologies, and links have been shown between TRIB proteins and liver and metabolic syndromes[73], neurodegenerative disorders[74]and inflammatory disorders[75]. Multiple unbiased genome-wide association studies (GWAS) have demonstrated associations between TRIB1 and plasmid lipid traits of relevance to cardiovascular disease[76,77]. Investigation into the role of TRIB3 in the progression of Parkinson's disease identified upregulation of TRIB3 in human patients and cellular models, with overexpression in cells sufficient to promote neuronal cell death via interaction with the pro-survival protein Parkin[74]. By contrast, TRIB3 expression in diabetic kidney disease reduces inflammatory gene expression[78].

Potential roles of TRIB biomarkers

Well-defined biomarkers are a crucial and powerful tool in disease classification, diagnosis, prognosis and clinical approach, emphasising the urgency for an ever-increasing library of biologically and clinically relevant markers.

Given the differential expression of TRIB proteins noted across cancer subtypes (**Error! Reference source not found.**) and the previously discussed TRIB1 R107L mutation, as well as additional diseases such as antibody-mediated allograft rejection[1], Parkinson's Disease[74] and inflammation[38], it is easy to appreciate the benefit of these proteins as potential novel biomarkers of disease and treatment.

TRIB2 has previously been reported as a biomarker for progression of melanoma[79], and multiple lines of investigation into its role in AML have supported its use as a biomarker of chemoresistance and relapse. In the AML cell line U937, elevated TRIB2 protein expression was demonstrated to directly correlate with high expression of the anti-apoptotic BCL-2 protein[2], which drives tumour survival and chemoresistance by

promoting proliferation and preventing apoptosis. Consequentially these cells were shown to be highly sensitive to BCL-2 inhibition with the BH3 mimetic Venetoclax and demonstrated synergistic killing when treated with a combination of Venetoclax and chemotherapy. This correlation of high TRIB2 and BCL-2 expression was further demonstrated in approximately 25% of primary patient samples, indicating that these results have clinical as well as biological relevance. Thus, use of TRIB2 as a biomarker can identify subsets of AML cells which are primed for cell death either with BH3 mimetics alone or in combination with chemotherapy, and in turn help to stratify clinical approach by identifying patients who may benefit most from this line of treatment.

Given the involvement of TRIB2 in the aetiology of cancers beyond AML, this observation raises an interesting question about the potential of TRIB2 as a marker in concurrence with BCL-2 elevation in other cancers. Existing data indicates high levels of BCL-2 expression in many cancers[80] including melanoma and lung cancer that exhibit high TRIB2 expression levels, and as such highlights the potential of TRIB2 as a biomarker for Venetoclax sensitivity in this context.

TRIB2 has also been highlighted as conferring resistance to standard therapies and PI3K inhibitors via a PI3K network, activating AKT and thus ablating FOXO and p53 activation. This corresponds to clinical outcome in metastatic melanoma, primary pancreatic and primary colon tissue samples, with TRIB2 (though not TRIB1 or TRIB3) expression correlating with a significantly worse prognosis[23].

Recently, TRIB3 expression in renal cell carcinoma was correlated with advanced tumour stage and unfavourable prognosis[67], with overexpression showing promotion of cell proliferation, migration, invasion and xenograft growth. Overexpression has also been positively correlated with VEGF-A expression and angiogenesis in gastric cancer[56], associated with a shorter survival time and higher incidence of recurrence and metastasis. In a pattern similar to TRIB2-related BCL-2 expression, this may highlight TRIB3 as a biomarker for subsets of patients who will be particularly receptive to treatment with VEGF-A inhibitors such as Votrient, which is currently used in the treatment of renal cell carcinoma.

Taken together these data emphasize the suitability of TRIB proteins as biomarkers for prognosis and treatment feasibility, helping to individualize patient treatment. This potential role extends beyond cancer malignancies; as discussed previously, GWAS analyses have demonstrated associations between TRIB1 and circulating alanine transaminase[81], which may function as a potential biomarker of fatty liver disease[82], further underpinning this proposed role. It is also clear that this hypothesis is not limited to the TRIB family, as pseudokinase members of the receptor tyrosine kinase family including ROR1, PTK7 and RYK have been found to have variable expression in subtypes of healthy and malignant B and T cells, implicating these pseudoenzymes as potential biomarkers for diagnosis[83].

TRIBs as alternative therapeutic targets

With their diverse functions in disease progression and prognosis, it is clear to see why TRIB pseudokinases also present an exciting possibility as therapeutic targets in addition to their function as biomarkers, and studies which have delineated the processes and pathways in which TRIBs are involved have also highlighted the therapeutic benefit of their depletion. In AML, TRIB2 depletion results in apoptosis, inhibited growth and cell cycle arrest[84], while in Parkinson's disease TRIB3 knockdown protects neuronal cells from death[74]. High expression of TRIB3 and its correlation with VEGF-A in gastric cancer highlight it's potential both as a biomarker as an antiangiogenic target[56]. Further, TRIB3 expression level was identified as a biomarker predicting the responsiveness to anti-acute promyelocytic leukaemia therapy and using tool peptide compounds to target TRIB3 protein interaction with PML-RARα enhanced anti-acute promyelocytic leukaemia therapy and had potent anti-leukemic efficacy[10].

Despite this, pseudokinases have been largely unexplored as drug targets due to the associated challenges, and currently no clinically approved therapeutics exist which target them. However, studies in their kinase counterparts may prove to be beneficial in developing this line of investigation. Structural studies investigating the non-catalytic roles of kinases have broadened our understanding of the molecular mechanisms supporting these roles[4,85] and have outlined that many functions are regulated by conformational changes in the kinase structure. This supports the hypothesis that there may be similarities in some non-canonical functions

between kinases and their pseudokinase counterparts, thus directing interest towards these structural characteristics as therapeutic targets[4]. In line with this, studies using small molecule compounds have demonstrated stabilization of the inactive state KSR-1 pseudokinase which antagonizes RAF heterodimerization and downstream Ras signalling[86], and HER3-targeting molecules modulate heterodimerization with active epidermal growth factor receptors and initiate partial degradation of the HER3 protein[12].

The lack of available crystal structures for TRIB2 and TRIB3 impedes investigation of structural changes as 'druggable' targets in these proteins, however the recently solved crystal structure of TRIB1 in complex with C/EBPα indicated that TRIB1 undergoes a substantial conformational change in its activation loop upon 'pseudosubstrate' binding[15]. This conformational change releases the COP1 binding motif from a binding site on the αC helix of the pseudokinase domain, effectively releasing TRIB1 autoinhibition while simultaneously binding C/EBP transcription factors for degradation (Figure 2). This result emphasises a potential therapeutic target outside of the canonical ATP-binding pocket; compounds targeted towards the TRIB 'active site' which can either stabilize or destabilize their alternative conformations could prove potent in affecting the lifetime and function of TRIB proteins in cells[15].

While we have chosen here to focus on the use of kinase inhibitor drugs, additional therapeutic options such as peptides or monoclonal antibodies also pose promising opportunities for treatment. The Pep2-S160 fusion peptide, for example, was demonstrated to disrupt the interaction of TRIB3 with PML-RARα[10] and advances have been made in the targeting of intracellular tumour-related antigens via their presentation on the cell surface by MHC-I[87].

TRIBs as a novel target in drug repurposing

The development of targeted therapy for cancer in recent years has produced a wide variety of anti-cancer compounds designed to target cancer-related molecules and signalling pathways. Of particular interest to the field of pseudokinases are kinase inhibitors, which bind to the ATP pocket and/or allosteric sites of oncogenic

kinases, impeding function with the goal of reducing aberrant growth factor signalling. Interestingly, many of these pre-existing drugs target pathways in which TRIB proteins have been demonstrated to play a role.

Repurposing of existing drugs presents a faster and more cost effective route of drug development than the development of novel compounds and thus recent studies have sought to investigate the potential of repurposing clinically approved drugs to seek out novel targets, including TRIB1 and TRIB2.

A recent study by Foulkes *et al* demonstrated the efficacy of three ErbB covalent kinase inhibitors Afatinib, Neratinib and Osimertinib in binding to and destabilizing TRIB2 *in vitro*[61]. This activity was mediated via competitive covalent binding to the conserved Cys^{96} and/or Cys^{104} residue located in the vestigial ATP-binding site of TRIB2, which confers protein stability under normal physiological conditions. Upon binding of ErbB inhibitors to this residue, TRIB2 was destabilized due to the uncoupling of the C-terminal tail, resulting in TRIB2 degradation facilitated by its own interactions with COP1. This demonstrates the dynamic nature of the docking of the C-terminal tail to the pseudokinase core, consistent with observations in kinase counterparts, and the potential of the vestigial ATP-binding domain as a novel target for TRIB2 inhibition. This study also highlights the potential of differential scanning fluorimetry (DSF) profiling in identifying clinically relevant secondary "on target" effects of currently approved drugs.

Similarly, as part of their structural studies of TRIB1, Jamieson *et al.* utilized DSF screening of published kinase inhibitors to identify compounds which induced thermal stabilization of TRIB1 by more than 2°C[15], indicative of a stabilizing interaction with the protein. By this method several compounds were identified, originally designed for targeting of either the vascular endothelial growth factor receptors or epidermal growth factor receptors, indicating that a similar approach to drug repurposing could be utilised in the case of TRIB1. Additionally, the discovery of the "SLE-in" and "SLE-out" conformational changes of the TRIB1 activation loop upon substrate binding raises an interesting possibility for small molecule targeting of TRIB proteins by targeting these changes in order to lock the protein into either of these configurations.

It should also be noted that in the emerging field of proteolysis-targeting chimeras (PROTACs), which exploits the endogenous proteasomes of cells by targeting proteins for degradation, structures often contain protein-

binding regions derived from kinase inhibitors[88]. It stands to reason then that PROTAC technology may indeed be adapted or repurposed for the targeting of pseudokinases and indeed the TX2-121-1 HyT degrader results in degradation of the HER3 pseudokinase and induces cell death of HER3-dependent cell lines[89].

Conclusions and future questions

We have highlighted existing research which provides evidence of TRIB proteins as a potential biomarker of disease progression and prognosis, with applications not only in cancer biology but in neurodegenerative and inflammatory disorders. Furthermore, we have outlined the potential of TRIB pseudokinases in stratifying patient treatment options. Whilst this has focused on the application of TRIB2 profiling in AML patients, it is clear that there are wider reaching implications for analysis of all TRIB proteins across varying cancer pathologies.

Additionally, although we have focused primarily on the TRIB family, the broader scope of these principals should not be disregarded. The HER3 receptor tyrosine kinase, for example, lacks appreciable kinase activity but is associated with several cancers due to its role as an epidermal growth factor receptor heterodimeric partner[12], thus having potential as a pharmacological target and biomarker for its associated cancers.

Moving forward it will be important to continue to recognize the roles of these 'inactive' proteins in order to identify those which may be employed as biomarkers in their associated conditions, and which can act as therapeutic targets. Furthermore, examination of the ability of existing drugs to target and diminish the activities of these proteins has the potential to yield important therapeutically-relevant results and aid in the improvement and ease of drug development and patient care.

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Figure 1. Structure and function of TRIB pseudokinase, with TRIB2 as a representative example.

An N-terminal PEST region mediates degradation to control protein turnover. A serine/threonine pseudokinase domain which lacks canonical kinase activity serves as a scaffolding region for substrate proteins, while the C-terminal region contains binding motifs for both MEK1 and COP1, mediating the MAPK pathway and E3 ubiquitin ligase respectively. Interactions with AKT have been demonstrated however the precise mechanisms of AKT regulation are unclear and vary between TRIBs.

Figure 2. Mechanism of action of TRIB1-mediated C/EBPα degradation by COP1. A) COP1-binding motif is bound to TRIB1 pseudokinase core in an autoinhibitory fashion. B) C/EBPα binding to core induces conformational change and releases COP1-binding C-terminus. C) COP1 binds to C-terminus via WD40 domain. D) COP1 mediates lysine ubiquitination of C/EBPα which is degraded by the proteasome. C/EBPα loss triggers release of COP1 by TRIB1 as inhibited conformation is resumed.

Figure 3. TRIB interaction pathways. TRIB proteins are involved both directly and indirectly with pathways which influence differentiation, apoptosis, cell survival, inflammation and senescence.

TRIB	Process	Reference
TRIB1	Liver function	[25–28]
TRIB1	Immunoglobulin production	[29]
TRIB1	Cell cycle control	[30]
TRIB2	ESC pluripotency	[31]
TRIB2	Thermogenesis	[32]
TRIB3	Adipogenesis	[33]
TRIB3	Glucose regulation	[34]
TRIB3	Cell cycle control	[35]
TRIB3	Neuronal apoptosis/autophagy	[36]
TRIB3	Lipid metabolism	[37]
TRIB1-TRIB3	Haematopoiesis	[13,38–42]

Table 1. Physiological roles of TRIB proteins in mammalian cells.

Cancer	Protein	Observations	Kinase inhibitors	Key references
Acute promyelocytic leukaemia	TRIB3	TRIB3 promotes progression and therapy resistance by suppressing PML-RARα degradation and inhibiting senescence. TRIB1 expression is decreased in human acute promyelocytic leukaemia.	SU11657, PP2	[10,46–48]
Breast	TRIB1, TRIB3	TRIB1 is overexpressed in triple negative breast cancer and regulates NF-κB and AP1-dependent transactivation of *CCND1.* TRIB3 overexpression confers good prognosis at the protein level, likely due to its inhibition of phospho-AKT.	Lapatinib, Canertinib, Abemaciclib, Neratinib, Olaparib, Palbociclib, Ribociclib, Talazoparib	[30,49]

Chronic lymphocytic leukaemia	TRIB1	Differential methylation in male vs female patients. Interactions with NF-κB pathway may contribute to more serious disease state in chronic lymphocytic leukaemia males.	Duvelisib, Ibrutinib, Idelalisib, Duvelisib	[50]
Colorectal	TRIB1, TRIB2	TRIB1 promotes cell migration via activation of MMP-2 via FAK/Src and ERK pathways. TRIB2 correlates with poor prognosis and blocks cellular senescence through AP4/p21 signalling. Also promotes resistance to therapy by activating AKT. TRIB3 is upregulated and increases expression of stem cell-related genes via interaction with β-catenin and TCF4.	Regorafenib, Vatalanib	[51–53]

Endometrial	TRIB3	Suppresses proliferation and invasion and promotes apoptosis via decreased expression of MMP-2 and MMP-9.	Lapatinib (with Trastuzumab Ab), Afatinib,	[54]
Thyroid	TRIB1, TRIB3	Significant overexpression noted in gene profiling.	Sorafenib, Lenvatinib	[55]
Gastric	TRIB3	Tumour angiogenesis and a poor prognosis, correlation with expression of VEGF-A.	Gefitinib, Erlotinib, Sorafenib, Sunitinib, Lapatinib	[56]
Glioma	TRIB1	Plays a critical role in the development of radioresistance due to complex formation with phospho-HDAC1 to suppress p53.	Imatinib	[57]
Hepatocellular Carcinoma	TRIB1	TRIB1 promotes hepatocellular carcinoma tumorigenesis and invasiveness via downregulation of p53.	Sorafenib	[58]

Leukaemia (myeloid)	TRIB1, TRIB2, TRIB3	MLL-TET1 (MT1), Notch1 and E2F upregulate TRIB2 via promoter binding. TRIB2 maintains differentiation blockade of myeloid cells. Confers chemoresistance by activating AKT. Both TRIB1 and TRIB2 bind to and degrade C/EBPα, and enhance ERK phosphorylation.	Bosutinib, Dasatinib, Enasidenib, Gilteritinib, Glasdegib, Imatinib, Ivosidenib, Midostaurin, Nilotinib, Ponatinib, Sunitinib, Afatinib, Osimertinib, Neratinib	[13,20,41,59–61]
Liver	TRIB2	TRIB2 promotes tumorigenesis and cell survival through interaction with the βTrCP ubiquitin ligase and degradation of C/EBPα.	Sorafenib,	[62]

Non-small-cell lung cancer	TRIB2, TRIB3	TRIB2 associates with TRIM21 E3 ligase to down-regulate C/EBPα. TRIB3 upregulation is associated with distal metastasis and disease recurrence, likely via Notch1/JAG signalling.	Gefitinib, Canertinib, Vatalanib, Osimertinib, Erlotinib	[63,64]
Ovarian	TRIB1, TRIB3	High TRIB1 expression was associated with a poorer survival rate likely due to activation of phospho-ERK.	Niraparib, Olaparib, Rucaparib	[65]
Pancreatic	TRIB2	Confers resistance to chemotherapy by activation of AKT pathway.	Erlotinib	[23]
Prostate	TRIB1	TRIB1 upregulation significantly associated with metastasis and poor prognosis.	Nilotinib, Erlotinib, Lapatinib, Imatinib	[66]
Renal cell carcinoma	TRIB3	Activated during hypoxia by HIF-1α and promotes cell proliferation, migration and invasion via MAPK.	Sorafenib, Sunitinib, Pazopanib	[67]

Table 2. Roles of TRIB family proteins in cancer subtypes, with associated clinically trialled kinase inhibitors and key references.

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Conflicts of interest

The authors declare no conflict of interest.